Coll. Antropol. **34** (2010) 2: 571–576
Original scientific paper

Ischemic Preconditioning Decreases Laparoscopy Induced Oxidative Stress in the Liver

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ABSTRACT

Experimental studies indicate that oxidative stress during and after laparoscopic surgery may cause liver ischemia-reperfusion injury. The aim of the study was to assess the effect of ischemic preconditioning against liver damage during pneumoperitoneum on oxidative stress. Twenty one New Zealand rabbits were divided into three groups of seven animals. Control group (C) rabbits received anesthesia for 60 min alone; 15 mm Hg intra-abdominal pressure with CO_2 for 60 min was used in the pneumoperitoneum group animals (PNP); and 15-min insufflation and 10-min desuflation followed by 60-min pneumoperitoneum were used in the ischemic preconditioning group animals (IP). Venous blood samples were obtained at different time points to measure lipid hydroperoxide, glutathione reductase and total antioxidant status as indicators of increased oxidative stress. Aspartate transaminase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) levels were evaluated as indicators of hepatocellular injury. The Kruskal-Wallis and Mann-Whitney U tests were used on statistical analysis. Elevated intra-abdominal pressure was found to produce significant increase in lipid hydroperoxide at the end of pneumoperitoneum and 30 min after desuflation in comparison with pre-insufflation period, and with both C and IP groups at the same time points. Total antioxidant status level decreased significantly in the PNP group at 24 h of desuflation. At 24h of desuflation, the AST, ALT and LDH levels were significantly increased in the PNP group in comparison with the levels measured before induction of anesthesia, and with the C and IP groups. Study results demonstrated that ischemic preconditioning prevented hepatocyte injury and oxidative stress during CO_2 pneumoperitoneum.

Key words: *laparoscopic surgery, oxidative stress, ischemic preconditioning*

Introduction

With the increasing use of laparoscopic surgery throughout the world, it has become apparent that intra-abdominal pressure above the normal physiological portal pressure (7–10 mm Hg) causes reduction in hepatic blood flow[1,2]. Disturbance of the hepatic blood flow alters liver function and this process might be further aggravated by desuflation at the end of the laparoscopic procedure. Pneumoperitoneum (PNP) and desuflation can be accepted as a typical ischemia-reperfusion (I/R) injury. Recent studies have shown that the free radicals released after blood flow restoration during desuflation are the most important mediators of oxidative tissue damage and consequential organ dysfunction, especially in the splanchnic organs such as liver[3–5].

Several methods have been proposed to prevent I/R injury after PNP with varying results, such as gasless surgery, fluid overload, and various pharmacological means. Recently, a procedure called ischemic preconditioning (IP), which ameliorates I/R injury by previous exposure to brief periods of ischemia and reperfusion before a prolonged period of ischemia, seems to be a rational approach. It is based on a delay in the injury processes involved in the development of I/R cellular injury and provides protection or tolerance against I/R injury[6].

Ischemic preconditioning was first described for the heart by Murry et al. in 1986[7]. Since then, the protective effects of IP have been demonstrated in various tissues

Received for publication May 12, 2010

such as kidney, bone, small intestine and lung. However, there are very limited data on the effects of preconditioning on the liver during PNP. Assuming PNP as an I/R model, we investigated the effects of IP on decreasing liver oxidative damage during and after laparoscopic procedures.

Material and Methods

A total of 21 New Zealand white rabbits weighing 1.6–3.3 kg were used in the study. Study protocol was approved by the Ministry of Science, Education and Sports, Ministry of Agriculture and Ethics Committee of the Department of Surgery, Orthopedics and Ophthalmology, Faculty of Veterinary Medicine, University of Zagreb, and followed national acts on the care and use of laboratory animals. The rabbits were housed individually in cages and unnecessary suffering was avoided. Animals were deprived of feeding for 12h before operation and had free access to water. All animals were anesthetized by intramuscular injection of ketamine hydrochloride 40 mg/kg (Narketan, Vetoquinol, Switzerland) plus xylazine 10 mg/kg i.m. (Xylapan, Chassot, Germany) and were allowed to breathe spontaneously during the experiments. Additional anesthetic doses (10 mg/kg im ketamine hydrochloride) were given when required during the procedures. After stabilization of anesthesia, animals were placed in supine position on a heating pad to maintain body temperature at 37°C. A 21 gauge catheter was inserted into the marginal ear vein and 22 gauge catheter into the auricular artery for blood gas analysis.

The operating field was shaved just before the operation, cleaned with 10% povidone iodide, and covered by sterile drape. PNP was created by placing a standard Veress needle, which was inserted supraumbilically, and the placement of the needle tip in the peritoneal cavity was confirmed by the saline drop test. Gas insufflation was performed by automatic device (Electronic-Laparofator Model 264300 200) at a rate of 2–3 L/min until the intra-abdominal pressure reached 15 mm Hg. In case of intra-abdominal pressure decrease due to transperitoneal CO_2 reabsorption, or in case of gas leakage from the trocar site, the device insufflated CO_2 automatically into the peritoneal cavity to keep the intra-abdominal pressure at the predetermined level.

The animals were divided into three groups of seven animals. Group C included control animals that only received anesthesia for 60 min, without intra-abdominal pressure increase; PNP group animals were subjected to 60-min CO_2 PNP; and IP group animals were subjected to 15-min insufflation and 10-min desuflation followed by 60-min PNP.

Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) were used as markers of hepatocellular injury. In all study groups, blood samples were obtained before anesthesia induction (baseline) and 24h after desuflation. Enzyme levels were measured by the classic kinetic UV method using a LISA 500 (Hycel Diagnostic) analyzer and results were expressed as unit/liter. Oxidative stress was assessed by measuring lipid hydroperoxide (LPO), glutathione reductase (GR) and total antioxidant status (TAS) in venous blood samples before anaesthesia induction; at the end of PNP and ischemia but before deflation/reperfusion (at 60 min); at 30 min of desuflation; and at 24h of desuflation/reperfusion. In control group, the same parameters were determined before anesthesia, at 60 min of anesthesia, and at 30 min and 24h of waking from anaesthesia.

TABLE 1
AST, ALT AND LDH LEVELS IN THE STUDY GROUPS BEFORE INDUCTION IN ANAESTHESIA (BASELINE) AND 24 H AFTER DESUFLATION OF PNP (R_2)

Group (n=7)				p value**		
	C	PNP	IP	C vs. PNP	C vs. IP	PNP vs. IP
ALT (25–65 U/L)						
Baseline	36.0±3.0	36.0±3.0	33.4±4.0			
R_2	39.9±3.8	94.7±6.*	36.1±3.5	<0.001	0.318	<0.001
AST (10–78 U/L)						
Baseline	16.4±1.8	15.7±1.8	17.7±1.1			
R_2	18.0±1.5	86.2±3.3 *	19.2±0.7	<0.001	0.534	<0.001
LDH (132–253 U/L)						
Baseline	124.4±27.6	138.9±27.4	132.2±16.4			
R_2	139.1±22.9	886.6±92.4 *	137.0±15.0	<0.001	1.000	<0.001

Baseline – before induction in anaesthesia; R_2 – 24h of deflation/reperfusion; C=control; PNP=pneumoperitoneum 15 mm Hg; IP=ischemic preconditioning
Data are expressed as mean±SEM
*Differences from baseline, Wilcoxon test, p=0.018
**Mann-Whitney U-test for group comparison

Data were analyzed with the STATISTICA for Windows, Release 6.0 program. Values were expressed as mean and standard deviation. Nonparametric variants were compared by Kruskal-Wallis test. When the analysis of variance showed a significant difference, the Mann-Whitney *t*-test was used. For analysis of data within each group, Friedman and Wilcoxon tests were used. The relations between serum enzyme levels and LPO and TAS values were evaluated using Pearson's correlation. A value of $p<0.05$ was considered statistically significant.

Results

There were no clinical signs of hepatic dysfunction or mortality in study animals and all rabbits were stable throughout the perioperative period. Results are presented in Tables 1 to 7.

In all groups, the baseline serum enzyme levels were within the normal range, with no significant between-group differences. A significant increase in AST, ALT and LDH as indicators of hepatocellular damage was observed in PNP group as compared with control group and IP group ($p<0.05$). When PNP was preceded by 15-min insufflation and 10-min desuflation (IP), the increase in ALT, AST and LDH was prevented. There were no significant differences in ALT, AST and LDH between the control and IP groups at any time point (Table 1).

In PNP group, serum LPO level as an indicator of free radical production was significantly increased at the end of PNP and 30 min of desuflation as compared to baseline level ($p<0.05$), peaking at 30 min of desuflation. However, LPO levels were similar in the control and IP groups, suggesting that the increase in LPO was also prevented by IP (Table 2). There were no significant within-group changes in GR activity during different stages of the experiment, or between the study and control groups at any stage in separate (Table 3).

TAS value showed a slight but non-significant decrease upon PNP desuflation and a significant decrease 24h postoperatively in comparison with PNP group baseline value. On group comparison, TAS value in PNP group was significantly lower than that in either control or IP group 24h after PNP desuflation (Table 4).

The relationship between serum liver enzyme levels and oxidative stress parameters measured at different time points was also investigated. Results of correlation analysis between serum liver enzymes at 24h of PNP desuflation and LPO increase are presented in Table 5. The strongest significant positive correlations were observed in PNP group between LPO at the end of PNP and ALT, AST and LDH 24h after PNP, with correlation coefficients of 0.892, 0.929 and 0.881, respectively. In addition, significant positive correlations were also recorded in PNP group between LPO 30 min of desuflation and ALT, AST and LDH 24h after PNP, with correlation coefficients of 0.848, 0.782, and 0.841, respectively. Hi-

TABLE 2
CHANGES IN LIPID HYDROPEROXIDE (LPO) LEVELS DURING THE STUDY PERIOD IN FOUR GROUPS (NMOL/L)

Group (n=7)	Baseline	p**	I	p**	R_1	p**	R_2	P**
C	2.33±0.04		2.38±0.04		2.40±0.02		2.44±0.06	
PNP	2.44±0.06	NS	2.61±0.07*	0.017 (PNP vs. C)	2.70±0.08*	0.004 (PNP vs. C)	2.57±0.08	NS
IP	2.33±0.05	NS	2.38±0.04	0.902 (IP vs. C) 0.011 (IP vs. PNP)	2.40±0.05	0.710 (IP vs. C) 0.007 (IP vs. PNP)	2.38±0.05	NS

Baseline – before induction in anaesthesia, I – at the end of PNP and ischemia but before deflation/reperfusion (at 60 min)
R_1 – 30 min of deflation, R_2 – 24 h of deflation/reperfusion
C=control; PNP=pneumoperitoneum 15 mm Hg; IP=ischemic preconditioning
Data are expressed as mean±SEM
* Differences from baseline, Wilcoxon test, p=0,018
** Mann-Whitney U-test for group comparison

TABLE 3
CHANGES IN GLUTATHIONE REDUCTASE (GR) ACTIVITY DURING THE STUDY PERIOD IN FOUR GROUPS (U/L)

Group (n=7)	Baseline	I	R_1	R_2
C	66.44±4.60	64.23±3.65	62.86±3.54	64.26±3.18
PNP	67.34±6.06	65.37±6.30	64.17±4.75	61.74±5.11
IP	57.80±2.12	56.98±1.99	55.90±1.93	56.00±1.57

Baseline – before induction in anaesthesia; I – at the end of PNP and ischemia but before deflation/reperfusion (at 60 min); R_1 – 30 min of deflation; R_2 – 24 h of deflation/reperfusion
C=control; PNP=pneumoperitoneum 15 mm Hg; IP=ischemic preconditioning
Data are expressed as mean±SEM. There were no statistically significant between-group differences.

TABLE 4
CHANGES IN TOTAL ANTIOXIDANT STATUS (TAS) DURING THE STUDY PERIOD IN FOUR GROUPS (NMOl/L)

Group n=7	Baseline	p**	I	p**	R_1	p**	R_2	p**
C	1.58±0.10		1.53±0.08		1.55±0.10		1.54±0.08	
PNP	1.63±0.12	NS	1.57±0.10	NS	1.55±0.11	NS	1.09±0.11*	0.017 (PNP vs. C)
IP	1.72±0.10	NS	1.68±0.09	NS	1.66±0.09	NS	1.62±0.09	0.456 (IP vs. C) 0.007 (IP vs. PNP)

Baseline – before induction in anaesthesia; I – at the end of PNP and ischemia but before deflation/reperfusion (at 60 min)
R_1 – 30 min of deflation; R_2 – 24 h of deflation/reperfusion
C=control; PNP=pneumoperitoneum 15 mm Hg; IP=ischemic preconditioning
Data are expressed as mean±SEM
*Differences from baseline, Wilcoxon test, p=0.018
**Mann-Whitney U-test for group comparison

ghly negative correlations were observed in PNP group between the levels of TAS and ALT, AST and LDH 24h after PNP desuflation, with correlation coefficients of –0.973, –0.921, –0.791, respectively (Table 6).

Discussion

Our study results demonstrated the 15 mm Hg PNP maintained for 60 min to be sufficient to create liver I/R injury, as manifested by a significant increase in LPO and transaminase levels, and a decrease in TAS. The degree of oxidative stress can be determined by directly measuring the activity of free oxygen radicals. However, because of their high reactivity, short life and instability, their activity is often determined indirectly by measuring the formation of oxidative byproducts or the concentration of antioxidants. Lipid hydroperoxide is formed under the action of free oxygen radicals in the process of lipid peroxidation and leads to destruction of the basic structure and integrity of cell membrane. Its concentrations have been proposed to be an important marker of I/R injury and an indirect measure of oxidative stress.

In the present study, a statistically significant LPO increase was recorded at the end of insufflation/ischemia; however, the values measured after desuflation/reperfusion were higher. As lipid hydroperoxide is an end-product of the oxygen free radical activity, study results confirmed the hypothesis that oxygen free radicals are being released during the early stage of reperfusion, suggesting that hepatic lesion sustained during reperfusion/desuflation might be more severe than the damage caused by ischemia/insufflation; in other words, it appears that reperfusion/desuflation does not protect hepatocytes from ischemia. Similar results have been reported by Kay et al.[8]. Measuring the concentration of malondialdehyde as another indirect indicator of free radical release, they monitored the effect of elevated intra-abdominal pressure and of gas desuflation on small intestine. The use of 60-min intra-abdominal pressure followed by gas desuflation resulted in a statistically significant malondialdehyde increase in the post-desuflation period. Measuring oxidative stress indicators, Glantzounis et al.[9] found the level of thiobarbituric acid to increase significantly 5 min after gas desuflation in patients undergoing laparoscopic cholecystectomy.

Besides LPO, the activity of GR as one of the major antioxidant enzymes was also assessed in the present study. Previous studies found the activity of antioxidant enzymes including GR to decrease in various tissues during prolonged I/R injury[10,11]. On the other hand, Portakal et al.[12] report on an increase of enzyme activities, attributing it to the formation of oxygen free radicals during

TABLE 5
CORRELATION BETWEEN LPO AT THE END OF PNP AND 30 MIN AFTER DESUFLATION AND SERUM LEVELS OF ALT, AST AND LDH 24 H AFTER DESUFLATION OF PNP IN EACH OF THE THREE STUDY GROUPS

	LPO (nmol/L) (end of PNP)						LPO (nmol/L) (30 min after PNP)					
	ALT		AST		LDH		ALT		AST		LDH	
	r	p	r	p	r	p	r	p	r	p	r	p
C	0.514	0.237	0.338	0.457	0.379	0.401	0.456	0.303	0.135	0.772	0.635	0.125
PNP	0.892	0.007	0.929	0.002	0.881	0.009	0.848	0.015	0.782	0.037	0.841	0.018
IP	–0.445	0.317	–0.584	0.168	0.373	0.409	0.008	0.985	–0.584	0.168	0.211	0.649

Pearson coefficient (r) are statistically significant at the 0.05 level
C=control group; PNP=pneumoperitoneum group; IP=ischemic preconditioning group

TABLE 6
CORRELATION BETWEEN TAS AND SERUM LEVELS OF ALT, AST AND LDH 24 H AFTER DESUFLATION OF PNP IN EACH OF THE THREE STUDY GROUPS

	TAS (U/L)					
	ALT		AST		LDH	
	r	p	r	p	r	p
C	–0.027	0.954	0.362	0.424	–0.165	0.723
PNP	–0.973	<0.001	–0.921	0.003	–0.791	0.034
IP	–0.316	0.490	–0.077	0.869	–0.057	0.902

Pearson coefficient (r) are statistically significant at the 0.05 level
C=control group; PNP=pneumoperitoneum group; IP=ischemic preconditioning group

I/R injury, i.e. the inability of antioxidant enzymes to neutralize the free radicals formed due to the short time of ischemia and reperfusion (only 30 minutes each). Other studies found no major change in GR activity during I/R injury[13]. Kobayashi et al.[13] monitored the effect of a varying length of hepatic ischemia and reperfusion on the glutathione redox system in an animal model. Animals were grouped according to the length of ischemia and reperfusion. There were no statistically significant changes from baseline GR activity, with the exception of the group with longest ischemia (180 min), where a statistically significant decrease was recorded. These results suggest the enzyme antioxidant activity to be lost upon reperfusion in case of prolonged ischemia; in other words, the decrease in GR activity upon reperfusion to depend on the length of ischemia. Our results are consistent with this study. As shown in Table 3, no significant changes of GR activity were recorded in any group of animals. The length of ischemia/insufflation was only 60 min and the time following reperfusion/desuflation 30 min. The results obtained may suggest that the amount of free radicals formed was inadequate to cause reduction of GR activity or the time of ischemia was too short to induce activation of this antioxidant enzyme. However, the reduction of total antioxidant capacity still suggested the amount of free radicals produced to be sufficient to activate some other antioxidant systems that ultimately led to TAS decrease at 24h of gas desuflation. Although Stipančić et al.[14] found no statistically significant TAS changes in patients operated on by either laparoscopic or open technique, Glantzounis et al.[9] report on TAS decrease 24h of laparoscopic cholecystectomy, which is consistent with our findings. Thus, an increase in LPO and liver enzymes and a decrease in TAS point to I/R injury of the liver.

As mentioned above, several preventive measures are recommended to reduce hepatic I/R injury. One of these measures is IP. Ischemic preconditioning is the most powerful endogenous mechanism that protects the organ against I/R injury by previous exposure to short cycles of ischemia/reperfusion[6] and increases tolerance to subsequent ischemic injury. The optimal time course of ischemia/reperfusion for IP varies among different organ systems and most literature data obtained from experimental studies indicate that the best effect on the liver is achieved by applying IP in cycles of 5/10, 10/10 and 15/10 min[15–18]. In the present study, we decided to apply IP cycle consisting of 15 min of ischemia followed by 10 min of reperfusion just before ischemia.

Although the beneficial effect of IP on the liver has been reported in many experimental studies[19–22], only a few studies in laparoscopic surgery are currently available. In 2003, Yilmaz et al.[23] published initial results on the effectiveness of IP in laparoscopic surgery. Their results demonstrated that IP consisting of 10-min insufflation followed by 10-min desuflation decreased the oxidative stress induced by sustained PNP in plasma, liver and kidney, and reduced ischemic damage to these organs after prolonged PNP. The same authors published another study showing that IP may also reduce intestinal oxidative stress injury following laparoscopic procedures[24]. Our results are in agreement with previous studies confirming that IP may prevent oxidative stress and preserve liver function in the early postoperative period.

The association of oxidative stress and hepatic function impairment should also be noted. In the present study, we monitored the correlation of liver enzyme activities 24h of gas desuflation and LPO levels at 60 min of PNP and 30 min of gas desuflation, i.e. at time points associated with a statistically significant increase of these indicators as compared with baseline levels. As shown in Table 5, a statistically significant correlation of liver enzymes and LPO was only recorded in the group of animals submitted to 15 mm Hg PNP without preconditioning (PNP group). Comparison of liver enzymes and TAS at 24h of gas desuflation from the abdominal cavity yielded a statistically significant but negative correlation between these parameters also exclusively in the PNP group (Table 6). The results suggested that this group developed highest oxidative stress level with consequential most severe liver function damage, whereas oxidative stress and consequential damage to the liver function was prevented in the group of animals submitted to IP. In addition, these results indicate that liver enzymes, although a nonspecific indicator of liver function, could be

used as a good indicator of hepatocyte ischemic injury irrespective of its etiology.

In conclusion, the results of our study suggest that, when PNP is applied at 15 mm Hg, the accumulation of oxygen free radicals elevates the level of LPO, a metabolite of lipid peroxidation, and decreases TAS, which may result in postoperative increase of liver enzymes. The present study also confirmed that IP treatment markedly suppressed the elevation of AST, ALT and LDH, thus potentially preserving liver function in the early postoperative period.

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ISHEMIJSKO PREKONDICIONIRANJE SMANJUJE OKSIDACIJSKI STRES JETRE IZAZVAN LAPAROSKOPSKIM OPERACIJSKIM ZAHVATIMA

SAŽETAK

Eksperimentalna istraživanja upućuju da tijekom laparoskopskih operacijskih zahvata dolazi do razvoja oksidacijskog stresa koji uzrokuje ishemijsko reperfuzijsku ozljedu jetre. Cilj istaživanja je procijentiti učinak ishemijskog prekondicioniranja na sprječavanje oksidacijskog stresa i posljedičnog oštećnja jetre tijekom pneumoperitoneuma. Skupina od 21-nog novozelandskog kunića podijeljena je u 3 skupine po 7 životinja. Kontrolnu skupinu (C) činili su kunići koji su bili podvrgnuti anesteziji u trajanju od 60 min; pneumoperitoneum skupinu (PNP) su činile životinje kod kojih je korišten intaabdominalni tlak od 15 mmHg postignut sa CO_2, a u skupini životinja sa ishemijskim prekondicioniranjem (IP) izvršena je insuflacija u trajanju od 15 min i desuflacija u trajanju od 10 min nakon čega se uspostavio pneumoperitoneum u trajanju od 60 min. U uzorcima venske krvi u određenim vremenskim razmacima određivani su lipidni hidroperoksid, glutation reduktaza i ukupni antioksidacijski status kao pokazatelji oksidacijskog stresa. Kao pokazatelji hepatocelularnog oštećenja određivani su aspartat transaminaza (AST), alanin aminotransferaza (ALT) i laktat dehidrogenaza (LDH). U statističkoj analizi korišten je Kruskal-Wallisov i Mann-Whitney U-test. Povišeni intraabdominalni tlak izazvao je značajno povećanje vrijednosti lipidnog hidroperoksida na kraju pneumoperitoneuma i 30 min nakon desuflacije plina u odnosu na prijeinsuflacijske vrijednosti te u odnosu na C i IP skupinu u istim vremenskim periodima. Statistički značajan pad ukupnog antioksidacijskog statusa zabilježen je 24 sata nakon desuflacije u PNP skupini. Dvadeset i četiri sata nakon desuflacije zabilježen je značajan porast AST, ALT i LDH u PNP skupini u odnosu na vrijednosti prije insuflacije te u odnosu na vrijednosti u C i IP skupini životinja. Dobiveni rezultati ukazuju da ishemijsko prekondicioniranje sprječava oštečenje hepatocita i oksidacijski stres tijekom CO_2 pneumoperitoneum.